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Expression of ADAM17 and its clinical value for patients with pernicious placenta previa

A retrospective study of 148 PPP patients underwent cesarean section

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Abstract

To explore the expression and the diagnostic value of ADAM17 in pernicious placenta previa (PPP) combined placental accreta. A total of 148 PPP patients were enrolled and divided into 2 groups: 62 patients with placenta accrete (PPP with PA group) and 86 patients without placenta accrete (PPP without PA group). In the same period, 74 pregnant women without PPP who had undergone cesarean section were selected as controls. The levels of ADAM17 were detected by qt-PCR. Diagnostic efficiency of ADAM17 were evaluated by receiver operating characteristics curve. ADAM17 was higher expression in PPP patients. Multivariate analysis showed that ADAM17 was related to gravida times (HR = 2.43 95% CI, 1.25–3.31), history of cesarean delivery (HR = 3.44, 95% CI = 2.24–4.28), history of abortions (HR = 2.22, 95% CI = 1.57–3.06) for PPP with PA patients and gravida times (HR = 2.01, 95% CI = 1.45–2.86), history of cesarean delivery (HR = 1.89, 95% CI = 1.33–2.48) for PPP patients without PA. Diagnostic efficiency of ADAM17 indicated that the sensitivity and specificity of ADAM17 detection for PPP with PA were 74.41% and 67.21% and for PPP without PA were 89.29% and 85.52%. Area under curve were 0.7876 (0.7090–0.8661) for PPP with PA and 0.9443 (0.9136–0.9750) for PPP without PA. Insummary, ADAM17 was higher expression in patients with PPP. ADAM17 was associated with gravida times, history of cesarean delivery, history of abortions. It also indicated a better diagnostic efficiency for patients with PPP. Further larger sample, multicenter studies should be conducted to confirm the conclusion from our study.

Abbreviations: 95% CI = 95% confidence interval, ADAM17 = A Disintegrin And Metalloprotease 17, AUC = area under curve, HR = hazard rate, PA = placenta accreta, PCR = polymerase chain reaction, PPP = pernicious placenta previa, ROC = receiver operating characteristics.

Keywords: ADAM17, cesarean section, diagnostic value, pernicious placenta previa, retrospective study

1. Introduction

Pernicious placenta previa (PPP) is often accompanied by abnormal relationship between placenta and uterine muscle wall, including placenta adhesion, implantation and penetration.[1] The occurrence of PPP may be related to the damage of endometrium at the implantation site of fertilized eggs.[2] During the early pregnancy, the endometrial stroma undergoes decidualization under the effect of ovarian hormones, and villi are implanted into the decidualized endometrium or decidua, forming the uterine placental blood circulation.[3] If the decidua of the uterus is primary dysplasia or damaged, the decidua at the bottom or the decidua sponge layer is reduced or absent, resulting in the chorion directly attached to the myometrium of the uterus.[4]

Pregnancy combined with PPP is likely to lead to premature delivery, DIC, hemorrhagic shock, placental abruption.[5] One of the most common consequences of PPP is massive hemorrhage during or after labor, with a incidence rate of about 53.9%, of which about 50% of patients have their uterus removed due to intractable massive hemorrhage, and about 7% of patients have died.[6] How to screen high-risk patients, effectively control bleeding, what kind of the most beneficial intervention measures to choose for patients with PPP are the most urgent questions to answer and solve at present.

At present, ultrasound examination is the most important and common method for prenatal diagnosis of PPP.[7] Although the sensitivity of ultrasound detection is 77 to 90% and the specificity is 71 to 98%, there is a certain misdiagnosis rate when the PPP combined with placenta accreta.[8] In recent years, some studies have used serum tumor markers in the clinical diagnosis of PPP with placenta accreta and achieved satisfactory results,[9] but the related clinical reports are still relatively

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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rare, and the specific threshold value of tumor markers is still uncertain. Therefore, this study aims to analyze the application value of ultrasound combined with ADAM17 in the diagnosis of PPP with placenta accreta.

2. Materials and methods

2.1. Study design

This research was designed as retrospective study. All of 148 pregnant women who were diagnosed with PPP and underwent cesarean section in the obstetric department from January 2020 to January 2021 in our hospital. The study was approved by the Ethics Committee of our hospital, and the patients and their families signed the informed consent form.

2.2. Patients selection

According to postoperative pathological examination, 148 PPP patients were divided into PPP with placenta accreta group (PPP with PA, n = 62) and PPP without PA (n = 86). Meanwhile, 74 healthy controls were included. The characteristics of PPP patients and healthy controls were showed in Table 1.

2.3. Inclusion and exclusion criteria

Inclusion criteria: (1) The placenta previa was confirmed as PPP by pathological examination; (2) there was a history of cesarean section, this pregnancy was placenta previa, and the placenta attached to the scar of the original uterine incision, with or without placenta implantation; (3) postoperative pathological specimens showed that placental villi were found in the myometrium of the uterus, which was diagnosed as placental implantation; (4) the patients in healthy control group were diagnosed as normal placenta; (5) all of included patients were singleton pregnancies, with complete clinical data and all of them were aware of this research protocol and signed a voluntary letter of commitment.

Exclusion criteria: (1) Patients with pregnancy induced hypertension, diabetes, intrahepatic cholestasis, and other pregnancy–related complications; (2) twin pregnancy; (3) patients with malignant tumor disease, blood system diseases, severe liver, and kidney diseases before pregnancy.

Table 1

Characteristics of included patients and healthy controls.

Characteristics	Healthy control (n = 74)	PPP patients (n = 148)		P
		PPP with PA (n = 62)	PPP without PA (n = 86)	
Age (Mean ± SD)	31.32 ± 6.18	31.27 ± 5.77	31.14 ± 5.96	0.174
Gravida times				
1	16 (21.62%)	8 (12.90%)	23 (26.74%)	<0.001
2	37 (50.00%)	42 (67.74%)	44 (51.16%)	
≥3	21 (28.38%)	12 (19.36%)	19 (22.09%)	
History of cesarean delivery				
0	11 (14.86%)	7 (11.29%)	14 (16.28%)	<0.001
1	46 (62.16%)	49 (79.03%)	47 (54.65%)	
≥2	17 (22.98%)	6 (9.68%)	25 (29.07%)	
Gestational weeks at delivery				
<37	8 (10.81%)	44 (70.97%)	49 (56.98%)	0.018
≥37	66 (89.19%)	18 (29.03%)	37 (43.02%)	
History of abortions				
0	52 (70.27%)	21 (33.87%)	37 (43.02%)	0.006
1	14 (18.92%)	33 (53.23%)	39 (45.35%)	
≥2	8 (10.81%)	8 (12.90%)	10 (11.63%)	
History of smoking				
Yes	6 (8.11%)	27 (43.55%)	31 (36.05%)	0.027
No	68 (91.89%)	35 (56.45%)	55 (63.95%)	
History of alcohol intake				
Yes	3 (4.05%)	15 (24.19%)	17 (19.77%)	<0.001
No	71 (95.95%)	47 (75.81%)	69 (80.23%)	
Type of PPP				
Marginal placenta praevia		4 (6.45%)	11 (12.79%)	<0.001
Partial placenta praevia		21 (33.87%)	34 (39.53%)	
Total placenta praevia		37 (59.68%)	41 (47.67%)	
Hospitalization (days)	3.21 ± 1.27	8.89 ± 2.35	5.93 ± 2.48	0.003
Intraoperative hemorrhage (mL)	149.45 ± 54.38	689.47 ± 75.16	311.29 ± 68.33	<0.001

PA = placenta accrete.

2.4. Laboratory tests

After the delivery of the placenta, 4 to 5 pieces of tissues of the maternal adhesion or implanted part of the placenta were selected in the PPP group and the middle part was selected in the control group avoiding the placental adhesion in the areas of hemorrhage, necrosis, and calcification. The volume of each piece is 1.0 cm × 1.0 cm × 1.0 cm, total RNA was extracted from the tissue and the expression level of ADAM17 was detected by fluorescence quantitative polymerase chain reaction.

RNA was diluted in RNase free water in order to obtain the same input template concentration (0.5 ng/μL for each reaction). Primer Assay kit protocol: reverse transcription at 50°C for 20 minutes, polymerase activation step at 95°C for 15 minutes followed by 3-steps amplification cycles (denaturation at 94°C for 15 s, annealing at 55°C for 20 s, and elongation at 72°C for 20 s). The $2^{-\Delta\Delta CT}$ method was used to calculating the expression level of ADAM17 mRNA.

2.5. Statistical analysis

SPSS 22.0 software was used for data analysis. The continuous variable data were expressed in Mean ± SD (x ± s). The data were compared by t test, the multiple groups were compared by 1-way ANOVA, and the pairwise comparison was performed by LSD t test. Counting data are expressed in [case (%)], and data comparison is made by χ^2 test. Pearson correlation coefficient method is used for normal distribution, Spearman rank correlation coefficient method is used for nonnormal distribution, and receiver operating characteristics (ROC) curve is used to evaluate the predictive value of ADAM17 for PPP. $P < .05$ indicates that the difference is statistically significant.

3. Results

3.1. Expression level of ADAM17 in patients with PPP

The expression level of ADAM17 mRNA in tissues was detected by polymerase chain reaction. Compared with healthy controls, ADAM17 was higher expression in PPP patients ($P < .0001$) (Fig. 1A) and there was also a significant difference between PPP with PA and PPP without PA in expression level of ADAM17 mRNA ($P < .0001$) (Fig. 1B).

3.2. The correction of ADAM17 expression level and characteristics of PPP patients

Univariate analysis showed that ADAM17 was related to gravida times (HR = 2.13, 95% CI = 1.57–3.02), history of cesarean delivery (HR = 3.18, 95% CI = 1.84–4.19), history of abortions (HR = 2.36, 95% CI = 1.44–3.15) for PPP with PA patients and gravida times (HR = 1.83, 95% CI = 1.12–2.32), history

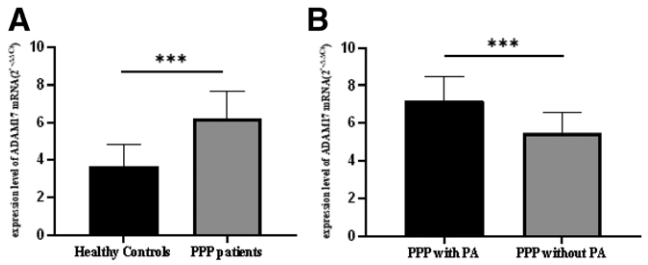

Figure 1. the expression level of ADAM17 in healthy controls and PPP patients. (A) ADAM17 mRNA expression level in healthy controls and PPP patients. (B) ADAM17 mRNA expression level in PPP with PA and PPP without PA. ***P < .0001. PA = placenta accrete, PPP = pernicious placenta previa.

Table 2

univariate analysis for correction of ADAM17 and characteristics of PPP patients.

	PPP with PA		PPP without PA	
Risk factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Gravida times				
≥3 vs ≤2	2.13 (1.57–3.02)	<.0001	1.83 (1.12–2.32)	<.0001
History of cesarean delivery				
≥1 vs 0	3.18 (1.84–4.19)	<.0001	2.14 (1.77–3.06)	<.0001
Gestational weeks at delivery				
<37 vs ≥ 37	1.23 (0.78–1.94)	.363	1.11 (0.96–1.38)	.388
History of abortions				
≥1 vs 0	2.36 (1.44–3.15)	<.0001	1.05 (0.79–1.35)	.249
History of smoking				
Yes vs No	1.06 (0.43–1.81)	.415	0.98 (0.43–1.21)	.416
History of alcohol intake				
Yes vs No	1.49 (0.88–2.47)	.286	1.27 (0.74–1.58)	.335

CI = confidence interval, HR = hazard ratio, PA = placenta accreta, PPP = pernicious placenta previa.

of cesarean delivery (HR = 2.14, 95% CI = 1.77–3.06) for PPP patients without PA (Table 2).

Multivariate analysis showed that ADAM17 was related to gravida times (HR = 2.43 95% CI = 1.25–3.31), history of cesarean delivery (HR = 3.44, 95% CI = 2.24–4.28), history of abortions (HR = 2.22, 95% CI = 1.57–3.06) for PPP with PA patients and gravida times (HR = 2.01, 95% CI = 1.45–2.86), history of cesarean delivery (HR = 1.89, 95% CI = 1.33–2.48) for PPP patients without PA (Table 3).

3.3. Diagnostic value of ADAM17 for patients with PPP

The diagnostic efficiency of ADAM17 was expressed by sensitivity and specificity, and the best cutoff value and reliability of the method are analyzed using the ROC curve. When taking 6.615 folds as the cutoff value of ADAM17, the sensitivity and specificity of ADAM17 detection for PPP with PA were 74.41% and 67.21% and for PPP without PA were 89.29% and 85.52%; ROC curve analysis revealed that the area under curve were 0.7876 (0.7090–0.8661, P < .0001) for PPP with PA (Fig. 2A) and 0.9443 (0.9136–0.9750, P < .0001) for PPP without PA (Fig. 2B).

4. Discussion

The diagnostic accuracy of color Doppler ultrasound for placenta previa is close to 100%, but it cannot accurately evaluate the degree of placental tissue invasion into uterine muscle

Table 3

Multivariate analysis.

	PPP with PA		PPP without PA	
Risk factors	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Gravida times				
≥3 vs ≤ 2	2.43 (1.25–3.31)	<.0001	2.01 (1.45–2.86)	<.0001
History of cesarean delivery				
≥1 vs 0	3.44 (2.24–4.28)	.005	1.89 (1.33–2.48)	.003
History of abortions				
≥1 vs 0	2.22 (1.57–3.06)	<.0001		

CI = confidence interval, HR = hazard ratio, PA = placenta accreta, PPP = pernicious placenta previa.

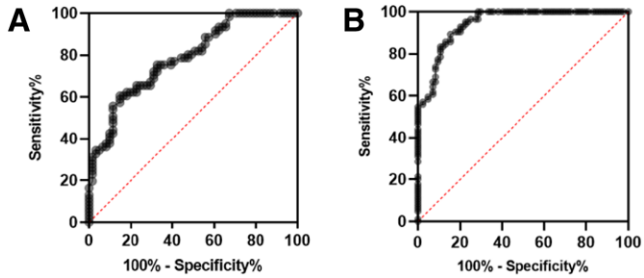

Figure 2. Diagnostic efficiency of ADAM17 for patients with PPP. (A) diagnostic efficiency of ADAM17 for patients with PA. (B) diagnostic efficiency of ADAM17 for patients without PA. PA = placenta accrete, PPP = pernicious placenta previa.

layer.[10] Furthermore, due to the placental position, weakness of uterine myometrium during pregnancy and other factors, it is difficult to observe the placenta in the posterior wall of the uterine body by ultrasound, and the diagnosis of PPP with placental accreta still has limitations.[11] PPP can lead to abnormal relationship between placenta and uterine muscle wall.[12] If it is not predicted or found in time, it may endanger the safety of mother and baby.[13] Therefore, it is of great significance to explore a reasonable and reliable examination method and the changes of related biochemical factors for the prediction, diagnosis, and treatment of placental accreta.

ADAM17 is a type I transmembrane protein containing multiple domains.[14] Its precursor domain can combine with zinc catalytic sites.[14] Only after the current domain is hydrolyzed by protein can ADAM17 have enzyme activity and participate in the hydrolysis of multiple proteins, such as TNF-α, transforming growth factor α (TGF-α), epidermal growth factor.[15] In recent years, studies have shown that ADAM17 is expressed in a variety of malignant tumors with a certain tumor cell specificity,[16] but less researches in gynecological diseases. Present study showed that ADAM17 was higher expression in PPP patients, and there was also a significant difference between PPP with PA and PPP without PA in expression level of ADAM17 mRNA. Multivariate analysis showed that ADAM17 was related to gravida times, history of cesarean delivery, history of abortions for PPP with PA patients and gravida times, history of cesarean delivery for PPP patients without PA. Diagnostic efficiency of ADAM17 was expressed by sensitivity and specificity, which indicated that the sensitivity and specificity of ADAM17 detection for PPP with PA were 74.41% and 67.21% and for PPP without PA were 89.29% and 85.52%. area under curve were 0.7876 (0.7090–0.8661) for PPP with PA and 0.9443 (0.9136–0.9750) for PPP without PA.

Although we designed present study as a retrospective study, there are still several limitations in this study. First, all patients included were Chinese, which may lead that the findings of this research may not be suitable for others from different countries.

Second, the sample size of this study was small. Further larger sample, multicenter studies should be conducted to confirm the conclusion from our study. Third, the potential mechanisms of ADAM17 could be well explored in in vivo and in vitro.

In conclusion, ADAM17 was higher expression in patients with PPP. ADAM17 was associated with gravida times, history of cesarean delivery, and history of abortions. It also indicated a better diagnostic efficiency for patients with PPP.

Author contributions

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